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BY

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PATHOLOGY OF DIABETES MELLITUS.*

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DIABETES mellitus is now considered by many authors to be a disease of more than one type and in this paper the classification of Lancereaux [1] will be adopted. He divides the disease into three forms, (1) constitutional, (2) nervous and (3) pancreatic. The symptomatology, pathology and experimental work which has been lately done on these varieties of diabetes will be here discussed, and an account of Chauveau's recent work given.

(1) The constitutional or fatty diabetes is the common form of this disease, and is well known to you all. It is most apt to occur in middle life, and frequently comes on in successive generations of a family, and cases are on record where it has been traced through four generations. Schmidtz [2] has traced heredity in 248 out of 600 cases of diabetes, and probably they were mostly of this variety. Obesity and gout are often precursors; and headache, epistaxis, hæmorrhoids and neuralgia are frequently prodromal symptoms. The disease begins insidiously, slowly advances, and often is accidentally discovered or brought to light by some of its characteristic complications. When discovered it rapidly yields to dietetic treatment, and after a residence at some resort like Carlsbad, the sugar may wholly disappear from the urine. It will return, however, in time, and the treatment must constantly be kept up. In these persons, the urine seldom rises above three or four litres per day, and the amount

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of sugar varies between 20 g. and 300 g. for the greater part of the time. This form of diabetes may have a long duration, and not greatly interfere with a man's business. Cases have lasted thirty and forty years.[1] Death comes either from an intercurrent disease or from the complications.

Unfortunately the pathology of this disease is not understood, and later investigations may destroy this classification.

Experimental work has added little to our knowledge of this type of diabetes. Considerable work, however, has been done on the so-called alimentary, toxic and phloridzine glycosurias, which will now be described.

Normal urine contains a small quantity of dextrose.[7] Experiments have been made on men and dogs to whom large amounts of sugar have been given. When 250 g. of cane-sugar were given to a man [3] who had been previously kept on a nitrogenous diet, 0.7 per cent. of the amount appeared in the urine. In dogs [4] the ingestion of such an enormous quantity as 500 g. caused 3 per cent. of the amount to appear. Eleven individuals [5] underwent a rather agreeable experiment in which they partook of a supper of sweets, ices and champagne. Two to four hours later the urine of five of the party contained from 0.1 per cent. to 0.25 per cent. of sugar. Two hours later the sugar had disappeared. Another writer [6] has found that animals which had been starved for a few days, when given small amounts of sugar experienced a transitory glycosuria. A similar lack of assimilation of sugar may explain light forms of diabetes. This is known as alimentary glycosuria.

Toxic glycosuria is due to the ingestion of various poisons, notably curare. A host of investigators have found sugar in the urine after injections of curare; but

an equally large number have affirmed that glycosuria was absent, providing artificial respiration was maintained. Halliburton [7] says that the glycosuria is not present in these cases, but that the sugar reaction is due to glycuronic acid. He furthermore adds that this explains the supposed glycosuria which sometimes follows the use of morphia and chloroform. Strychnia, nitrate of uranium and many other drugs are claimed to have the power of bringing about a temporary glycosuria.

Phloridzine glycosuria has excited much interest. When phloridzine is given to an animal in the food, or subcutaneously, a glycosuria is produced. It commences about three hours after the ingestion of the glucoside, attains a maximum in twenty hours, and ceases within a day and a half. The glycosuria varies with the amount of food ingested. Various explanations of this phenomenon have been offered, but a recent series of experiments by Minkowski and von Mering throw much light on the subject. In birds glycosuria does not follow extirpation of the pancreas, but von Mering [8] found on giving phloridzine that sugar appeared in their urine. Dogs rendered diabetic, passed an additional amount of sugar when they were given the drug. This led Minkowski to make the following experiment.[8] He removed the kidneys, both from a healthy dog and from a dog suffering with diabetes produced by pancreatic extirpation. To the healthy dog he gave phloridzine. After a time the blood of both animals was examined. The diabetic animal's blood contained 0.3 per cent. to 0.5 per cent. of sugar, which is from two to three times the normal quantity, while the phloridzine animal showed an abnormally small amount of sugar in the blood. He argues that if sugar is being formed in the organism, removal of the kidneys, thus preventing its excretion,

will cause a storing up of it in the blood. The experiment shows that in the diabetic animal this was done, while in the phloridzine animal the sugar, far from being increased, was diminished. He, therefore, concludes that the glycosuria produced by phloridzine is due to its direct action on the kidneys.

In considering this constitutional type of diabetes, with regard to which we know so little, it is well to remember that an excessive amount of carbohydrates and some poisons may cause a temporary glycosuria, and that the kidneys under certain circumstances may allow the passage of sugar.

(2) The nervous or traumatic [1] variety of diabetes is the mildest of the three forms. It comes on after shock to the nervous system caused either by trauma or some severe mental strain, for example, worry, anxiety and the like, and runs a variable course. Polyphagia is absent, and the patient is seldom troubled with polydipsia. The urine is perhaps twice the normal amount, and though sugar is present, it is not in large quantities. There is little loss of weight. Subjected to treatment, hygienic and dietetic, the individual rapidly recovers, and the transitory glycosuria is over. Complications are rare. There is a sure tendency to recovery, and death almost never occurs unless there are extensive lesions of the central nervous system.

Pathology. — The pathology of the nervous form of diabetes has been earnestly studied and with good reason, for clinically mental disturbance appears to play a great rôle in its etiology. Packard [9] says many railroad engineers are victims to this disease. Paige [10] lays great stress on mental emotions. Madigan [11] has observed glycosuria alternating with insanity in a patient. Savage [12] has found diabetes and insanity alternating in families. Nagel [13] has observed two cases of persistent glycosuria following an apoplectic attack.

Dr. R. H. Fitz [14] referred to the presence of glycosuria in epilepsy. Windle [15] has tabulated the records of 184 brain examinations in the post-mortems of diabetic persons. In 91 instances, the brain was normal; and of the remaining 93, 23 were connected with the fourth ventricle. These lesions were of the most varying type; cerebral hæmorrhage, meningitis, tumors and congestion of the blood-vessels were all noted.

The whole subject was looked into by a committee of the London [16] Pathological Society in 1882, who reported that they failed to find in the brain "any change which could be regarded as exclusively or constantly associated with diabetes."

In 58 cases of diabetes in which an examination of the spinal cord was made, 37 were found normal; and in the remainder there was no characteristic lesion.[15]

Experimental Work. — The experimental work of Claude-Bernard, on the production of glycosuria by the puncture of the fourth ventricle, was one of his most brilliant achievements. This has been repeated many times with success. If the medulla be punctured in the region of the vaso-motor centre of a well-fed animal, sugar will appear in the urine in considerable quantity. After a few hours the sugar will have reached a maximum, and in a day or two, or even less, the sugar will be absent from the urine. If the animal has been starved previous to the experiment, little or no sugar appears. It would thus seem likely that the lesion to the fourth ventricle in some way acted on the liver so that the change of glycogen into sugar was accelerated, and the blood thus loaded with sugar emptied its excess into the urine.

The pneumogastric nerves [17] run to the liver, via the solar and hepatic plexuses. Section of these nerves does not give rise to glycosuria, nor does stimu-

lation of the peripheral end of the section. This shows that the impulse from the diabetic centre in the medulla does not travel along these nerves. On the other hand, electrical stimulation of the central end of the section produced a glycosuria analogous to that brought about by puncture of the medulla. Furthermore, it is claimed that in some cases an irritation of the branches of the tenth pair of cranial nerves in the abdomen, liver, lungs, heart, stomach and intestines may in some cases bring about a temporary appearance of sugar in the urine. This would imply that the pneumogastric exercises an inhibitory influence upon the diabetic centre of the medulla.

The liver receives another nerve-supply through the splanchnics. When these nerves are cut, no sugar appears in the urine ; and if then the diabetic puncture is made, it fails. Evidently, the action of the diabetic centre on the liver is by means of the splanchnic nerves. These have been traced to the spinal cord, with more or less probability, through the gangliated cord of the sympathetic, the first dorsal ganglion, the annulus of Vieussens and the lower cervical ganglion. Probably they do not leave the cord always at the same level.

Lustig obtained a transitory glycosuria by making lesions of the solar plexus, and Lepine has produced diabetes by electrization of the nerves of the pancreas. "Section and subsequent stimulation of the central end of the sciatic nerve causes diabetes." [18]

With regard to these experiments on the nervous system, I should like to call your attention to the following considerations : (1) the glycosuria has been transitory in every case ; (2) the experiments are severe, and might of themselves produce such a constitutional derangement that glycosuria would result, even if there was no injury to the nerves ; (3) as for

an injury of the solar plexus producing glycosuria, Minkowski has shown this view to be erroneous. The work of Chauveau on nerve lesions is so recent that it will be deferred to the end of the paper.

(3) The pancreatic or thin type of diabetes is the most severe form of diabetes mellitus. In one class of cases, an individual who has been in perfect health is plunged into the midst of a severe diabetes. In other cases the symptoms come on gradually; and belching of wind, nausea, a sense of fulness and weight in the epigastrium are often the first indications of trouble. Diarrhœa is often present. In still other cases, what is supposed to be a fatty diabetes develops into the thin variety.[19] When the disease is established the polyphagia, polydipsia and polyuria are extreme. The skin is harsh, dry and leathery to the touch. Emaciation quickly comes on, and there is great fatigue on exertion. The knee-reflex is usually abolished. Often the hair is lost, and the patient's teeth decay or fall out. The mental character is changed, and the unhappy individual is often in a state of mental depression. Hectic fever has been observed. The evolution of the case is characterized by its rapidity, and in the course of a period from a few months to three or four years, the patient usually succumbs to phthisis or diabetic coma. The urinary symptoms are much more severe than in either the fatty or the nervous forms. The quantity ranges between three and ten litres, and is generally between five and seven. The urea is decidedly increased and the sugar excreted per day is from 300 g. to 500 g.

Pathology. — Thomas Cowley,[20] in 1788 was the first to record a lesion of the pancreas in connection with diabetes mellitus. He observed an atrophy of the gland, with the presence of calculi, and suggested that it might be the cause of the disease. During in-

tervals of forty years, more or less, Chopart[20] and Recklinghausen[20] made similar observations. But it was not until 1877 and the few following years, that the matter received much attention. Lancereaux[1] then published his two cases. In one of these the pancreas was atrophied, and much of the glandular structure was lost; in the other it was only with difficulty that the gland was found at all; but when found, calculi were discovered in the canal. Lancereaux's memoir led pathologists to study the pancreas more carefully; and, as a result, in quite a number of instances of diabetes, pancreatic lesions have been found. There would undoubtedly to-day be more recorded cases of changes in the pancreas in diabetes, were it not for the fact that the gland may look perfectly normal to the naked eye and yet on microscopical examination show marked alterations.[20 31] Until this becomes more generally known, a diseased pancreas will be often overlooked.

What is the character of these changes? They are most varied, but the predominating characteristic is an increase in the amount of interstitial tissue. Williamson[19] has collected 100 cases from the literature upon the subject; 47 showed an atrophy more or less marked, and of this number the gland was almost absent in three; in two others it was not recognized by the naked eye, and in two there was a cystic dilatation of the duct. Seventeen out of 100 were in a condition of marked fatty degeneration; and in some instances an increase of the connective-tissue, the presence of calculi or atrophy were coexistent with the main lesion. In another group of 13, the gland was transformed into a firm mass of fibrous tissue; in three of this number the lesion is stated as a marked cirrhosis. Of the remaining cases eight were cancer, six were cysts and three abscesses. There were two

cases of "pancreatitis and pancreatitis hæmorrhagica," and one each of calcified, cirrhotic and cystic pancreas, while in the remaining case the occurrence of calculi was alone stated. Rokitansky [19] found the pancreas affected in 13 out of 30 cases. Saundby [21] gives seven cases in which the pancreas was atrophied and four where it was abnormally firm and fibroid. Windle [15] collected post-mortem records on the pancreas in 139 cases. In 65 of the number, the gland was normal. Lest some of his cases and those of Williamson may be identical, I will pass them by, simply stating that atrophy and fatty degeneration were the most common affections.

Are these changes in the pancreas which are found in diabetes accidental? Are they the result of the disease? Do they furnish the cause of one form of this malady?

The first question can be answered in the negative with a good deal of assurance. Pancreatic changes have been found too often in connection with diabetes to be accidental. It does not seem likely either, that they are the result of the disease. They are too diversified to have a common origin. That they are concerned intimately with the production of diabetes, their frequency and the experimental work done on the pancreas makes highly probable.

Experimental Work. — The experimental work of Herr von Mering and Herr Minkowski,[8] on the production of diabetes by pancreatic extirpation, forms one of the foremost chapters in all experimental pathology. It is about two hundred years since Wirsung gave his name to the pancreatic duct. The pancreas must have excited a good deal of interest at that time, as we find Regnier de Graaf [22] and Conrad Brunner [22] trying to extirpate it. They thought that their attempt was successful, and published two articles, in which

the medical fraternity was informed in Latin that the removal of the pancreas was provocative of no results. Their word was accepted — or forgotten; and I find no further mention of the subject until Claude Bernard attempted to produce a diabetes by plugging the duct of Wirsung, and failed. In 1889 von Mering and Minkowski began their work on the subject, to which they have added from time to time ever since. Many investigators have confirmed their work, but none have essentially added to it.

The technique of the removal of the pancreas is no mean piece of surgery. The gland is difficult to get at, the blood-supply is free, and it has an intimate connection with the surrounding parts. The total removal is essential for the success of the experiment, and it is in this particular that so many have failed. So carefully has Minkowski conducted his operations that in not a single instance did he leave even a small part of the pancreas in the abdomen. Peritonitis is one of the greatest bugbears to the operation. After full extirpation, first intention is seldom obtained, though this was obtained in partial removal of the gland. The experiments have been conducted on dogs. Cats are difficult to experiment upon, and the pancreas of rabbits cannot be successfully removed. Good results come from the extirpation in swine, but in birds and frogs the returns are not so satisfactory.

When a healthy dog is deprived of the pancreas he is attacked invariably within twenty-four hours with glycosuria, which continues for some weeks without interruption up to the death of the animal. On the first day after the operation the urine contains one per cent., or less, of sugar; on the following day the percentage has risen to four or six; and on the third day it has reached eight, ten, or even more. If no food is taken, the sugar begins to diminish; but after seven

days of starvation it does not fully disappear. The amount of sugar decreases when the animal becmes very weak, and at some time before death may wholly disappear from the urine. In two of Minkowski's cases this occurred. "The diminution in the amount of sugar excreted in no way corresponds to an improvement, but rather to a worse state of the conditions of nutrition." Peritonitis and septic processes may lead to a disappearance of the sugar. If carbohydrates are taken, the amount of sugar rises rapidly, and the sugar ingested is practically wholly excreted. The urea stands to the sugar in the ratio of two to three, when the dog is on a pure flesh diet; and this ratio is maintained with very slight variations through all the vicissitudes of the experiment. Thirst, polyphagia and polyuria are constant accompaniments of the glycosuria; and the emaciation, feebleness and the slow healing of the wound all show that the animal is suffering from a severe diabetes mellitus.

Von Mering and Minkowski have further reported that after a partial extirpation of the pancreas a diabetes was not produced. To this fact they attach much importance. They think this explains the non-appearance of glycosuria in man in some pancreatic lesions. A part of the gland can perform the function of the whole. Furthermore, this answers the objection which has been raised that the diabetes was due to nerve lesions caused in the operation. In the removal of a large portion of the gland, for example, four-fifths, the same nerve lesions would be committed as in the removal of the whole gland. Just how much of the gland must be left in the abdomen to prevent diabetes cannot definitely be stated. The nutrition of the part left behind here enters into the problem. In some of the instances where a portion of the gland is removed, a diabetes of light grade is produced. This is present

only when the animal is on a carbohydrate diet: and it is supposed that slight glycosurias in man might be attributable to some moderate disturbance of the pancreatic function.

The abdominal grafts of the pancreas are by far the most striking part of Minkowski's and von Mering's work. This was suggested by Schiff's work on the thyroid. The art of the experimenter is here given full range. The pancreas is a fragile organ and quickly dies. Moreover, an animal which has submitted to an operation on the gland is in great danger of peritonitis. Both obstacles were overcome in the following manner. The pancreas was carefully dissected from its attachments in the abdominal cavity, turned on its axis and stitched to the abdominal wall. The blood-supply was disturbed as little as possible. The wound was allowed to heal, and gradually the pancreas became engrafted on its new surroundings. When this was firmly established the dog was submitted to another operation, in which the internal part of the gland was removed. On the recovery of the animal no diabetes resulted. After an interval of some time, the engrafted pancreas was removed; and when this was done, diabetes in all its forms appeared. What more striking proof could be asked for the action of the pancreas in producing diabetes?

The removal of the graft with its sequence of diabetes throws aside completely the theory that in these cases nerve lesions are the cause of the disease. The blood-supply of the graft, in some cases from the abdominal parietes, in others from the aorta alone, excludes any theory which ascribes the prevention of the diabetes to the different blood-supply the gland might receive.

No connection exists between the intestinal secretion of the gland and its functions in the prevention of glycosuria. Minkowski has observed the absence of

the ordinary secretion and yet no diabetes, while Thiroloix [24] has seen a diabetes come on when the secretion was active.

Is this function whose disturbance leads to the production of diabetes a specific property of the pancreas? Minkowski concludes that it is, else why should diabetes appear on its extirpation? Various authors have thought differently. Renzi and Reale [28] found sugar in the urine after the removal of the salivary glands. Minkowski has carefully gone over their work in his own laboratory and finds (1) that the glycosuria was usually slight in intensity, (2) that it was transitory, and (3) that it was not even a constant result of such extirpation. And as for the work of the same authors on duodenal extirpation, much the same conclusions were reached which Weintrand [25] has further confirmed.

Falkenberg, after removal of the thyroid, obtained a glycosuria in 13 out of 20 cases. Gley [26] and Minkowski agree in thinking this glycosuria due to traumatism.

It may be well to definitely state that the removal of the gland so that all intestinal secretion is cut off brings on no diabetes. A transitory glycosuria may result from the abdominal operation.

Minkowski's experiments of total extirpation, partial extirpation and grafts of the pancreas have been confirmed by Hedon,[27] Thiroloix [28] and Abelman.[22] Lepine [29] in 100 pancreatic extirpations, and Sandmeyer [30] in 29, have come to the same result.

How does removal of the pancreas cause diabetes mellitus?

Minkowski does not say, but simply states the two theories which are advanced, and points out that there are further channels for experimental work which when traversed will enable us to have a clearer insight into the question.

The first of the two theories at present most advocated is that there is a ferment in the blood which destroys the sugar. This ferment is furnished by the pancreas, disease or removal of which causes a heaping up of the sugar in the blood, due to the non-assimilation of the sugar by the tissues. The other theory implies a poison in the blood, which in the normal person is destroyed or rendered inactive by the pancreas; removal of this gland allows an accumulation of the poison and grave nutritional disturbances.

Lepine [31] was a fellow-worker with Dr. H. P. Bowditch, who has spoken highly of him to me as a scientist. He discovered that the normal pancreas when treated with a little water made alkaline was able to destroy a small quantity of sugar. The blood of an animal deprived of its pancreas lost less sugar than the blood of a sound animal; and hence Lepine concluded that the pancreas yielded to the blood a ferment which contributed powerfully to the destruction of the blood sugar. This ferment he called the glycolytic ferment. He found that the blood of the portal vein was richer in this ferment than that of any other part of the body, and after an elaborate series of experiments proved that this ferment was contained in the white blood-corpuscles. This ferment is diminished, he has shown, in the blood of diabetic persons to the number of seven; and, in fact, in all cases in which there is an increased amount of sugar in the blood the ferment is present in less than the normal quantity.

Writers on diabetes speak favorably of Lepine's theory, but most of the experimenters have not yet accepted it. This theory of Lepine's necessitates the view that glycosuria results from the lack of the power of assimilation of the sugar by the body. Hedon [27] and Seegan [32] also consider that the lack of assimilation of the sugar is the cause of diabetes.

RECENT WORK OF CHAUVEAU.[33]

Chauveau was a fellow experimenter with Claude-Bernard. He has done much eminent work in time past, and the field of experimental diabetes is well known to him. Two articles which he has recently published connect the work of Claude-Bernard and that of Minkowski. In his first memoir he proves that diabetes is due to an increased production of sugar by the liver. In a normal animal the blood in the hepatic veins contains the most sugar of any blood in the body. The sugar in the arterial blood always is greater in amount than that in the venous. Claude-Bernard has shown the formation of this sugar to be the property of the liver, and Chauveau has made clear that the destruction of the sugar takes place in the tissues. Somewhere in the capillaries between the red arterial and dark venous blood the sugar is lost. If this sugar continues to be lost in an animal rendered diabetic, we can feel sure that the cause of the diabetes rests on the overproduction of sugar and not on its lack or destruction.

So Chauveau produced diabetes in animals by traumatism, by puncture of the fourth ventricle, by section of the cord just below the medulla and by removal of the pancreas. In each instance the analysis of the arterial and venous blood showed the normal excess of sugar in the former. It is well known that a section of the spinal cord from the last few cervical to the sixth dorsal vertebræ produces a diminished amount of sugar in the blood; but when this section was made, the arterial remained richer in sugar than the venous blood. His experiments confirmed his theory that diabetes is due to an increased production of sugar. This work was preliminary to his next article.

We know that sugar is formed in the liver. Is it

formed anywhere else? The muscles remove the sugar from the blood, which they use dehydrated in the form of glycogen. There is no reason why these, like the liver, should not convert this glycogen back into sugar, but no proof of this has ever been given. Furthermore, if the muscles did do this, we should expect to find more sugar in the venous blood than in the arterial, but Chauveau's previous work has shown that this is not so. The liver, then, is the source of the increased sugar in the blood — hyperglycémie — in diabetes; and if we can explain the mechanism by which the liver brings this about, we can explain the disease.

For a long time it has been known that puncture of the fourth ventricle would produce a passing glycosuria, and lately von Mering and Minkowski have shown that removal of the pancreas will cause the same result. Various clinical facts also go to show that the pancreas is connected with the production of diabetes. And this leads us to consider the pancreas in a new light as a moderator of the glycæmic function of the liver. Now in diabetes there is besides the glycæmia a destruction of the tissues going on throughout the entire body. The losses of the body surpass its gains. Katabolism is the ruling feature, and from the products resulting from the katabolism part of the sugar is formed in the liver. This we know because diabetic animals which are starved still continue to secrete sugar. But how does the pancreas act to prevent this destruction of tissue and subsequent formation of sugar in the normal state? As the veins of the pancreas empty into the vena porta, it is natural to explain this influence of the pancreas upon the formation of sugar in the liver by supposing an internal secretion of the gland which empties into the blood, by which it is carried to the liver and participates in its functions. However, as

yet experiment has given no proof of the direct action of this pancreatic secretion on the liver. The facts already known, with what Chauveau adds later, tend to show that this action is through the agency of the nervous system.

The functions exercised by these two glands depend without doubt upon their inherent properties, but the nervous system cannot fail to regulate their action. Glands have been shown to have excito-secretory nerves — compare the submaxillary gland and the chorda tympani — and there is no reason to suppose that the pancreas and the liver are exceptions. In fact the teachings of physiology would impose upon us the consideration of the existence of excito-secretory and inhibito-secretory nerves of the liver. Indeed, study of nervous action on the liver has been made; but Chauveau combines the former experiments with pancreatic extirpation.

When a section of the spinal cord at its junction with the medulla was made on starving dogs, hyperglycémie resulted as after the extirpation of the pancreas and this hyperglycémie was attended with glycosuria. These common symptoms lead us to draw a connection between the result obtained on bulbar section and pancreatic extirpation, and to conclude that in both instances the animal is subjected to the same influence; in one, pancreatic secretion is rendered impossible by removal of the pancreas; in the other, it is made quite as impossible by paralysis of the gland. From the effects thus produced by bulbar section we can conclude that the pancreas is thereby isolated from its excito-secretory centre, whence suppression of the internal secretion and subsequent hyperglycémie. But this section did not injure the excito-secretory centre of the liver; on the contrary, it became more active, which would imply that it was not antagonized. The

following deductions then can be drawn from bulbar section: (1) the action of the pancreas on the glucose-forming function of the liver appears to be under the control of a centre which excites the internal secretion of the pancreas; (2) this centre is situated at some point above the junction of the cord and medulla; (3) the sugar-forming function of the liver is controlled by an excito-secretory centre which is situated in some region of the spinal cord; (4) the action of the pancreas upon the liver is exercised upon the excito-secretory centre of the liver and not on the liver itself.

Puncture of the fourth ventricle causes much the same train of phenomena as does the section of the cord at its junction with the medulla. In bulbar section the animal of course dies because his life is dependent on artificial respiration. In medullary puncture respiration is not disturbed. The identity of the results leads us to consider that in sugar-puncture of the fourth ventricle the excito-secretory function of the pancreas is for the time deranged. This leads up to the conclusion that this centre is no higher up in the nervous system than the medulla, and the section between the spinal cord and medulla has shown that it is no lower.

This production of glycosuria by bulbar section can also be explained on the hypothesis that there is an inhibito-secretory centre of the liver in the medulla, which by the operation is shut off from its influence on the liver. The internal secretion of the pancreas then would stimulate the inhibito-secretory centre and moderate the excito-secretory, while its absence would produce just the opposite results and hyperglycémie would appear. The lighter glycosuria which appears on bulbar section could then be explained by the pancreas acting to a slight extent, though removed from its excito-secretory centre. Having thus set forth the

theory, Chauveau proceeds to the more original part of his work.

When a section of the cord is made between the fourth cervical and sixth dorsal pairs of nerves, a hypoglycémie is produced. Evidently this is due either to increased action of the inhibitory centre or paralysis of the excitatory. The second alternative conforms more easily to the facts. Now as this paralytic effect ceases when we go above the fourth cervical pair, and we then get hyperglycémie, it is evident that the excito-secretory centre of the liver is in the neighborhood of the fourth cervical pair. The section between the fourth pair cervical and sixth pair dorsal is then explained by this section severing the communication of the excito-secretory centre with the liver. It can furthermore be deduced that the inhibitory fibres of the liver pass out of the cord above the fourth, or else the hypoglycémie would not result from section below that point.

When a section between the fourth cervical and sixth dorsal is followed by removal of the pancreas, instead of getting a hyperglycémie with the symptoms of diabetes which are ordinarily obtained on removal of the pancreas, Chauveau found a condition of hypoglycémie, and following the theory as detailed above, the explanation is easy. The connection between the liver and its excito-secretory centre having been severed, the removal of the pancreas could not produce its ordinary effects.

When suppression of the pancreas is followed by section of the cord between the fourth cervical and sixth dorsal, from the previous work we should expect that the symptoms of diabetes would cease when the latter part of the operation was performed; but no such result awaits the experimenter. The hyperglycémie continues. The reason can be found in the

sympathetic ganglia which lie in the track of the nerves. These act as relays to the central nervous system; and from these nervous impulses are sent forth, only these are dependent in character upon the primary impulse which is received from the higher source. They continue to act in the same way even though separated from their centres in the central nervous system. So when the cord was cut between the fourth cervical and sixth dorsal, the ganglia were left under the control of the inhibitory centre, and subsequent removal of the pancreas had no effect.

These experiments are further varied by substituting the bulbar section for removal of the pancreas, and the same results are obtained. Thus, section of the cord between the fourth cervical and sixth dorsal, followed by section at juncture of medulla and cord, produces no hyperglycémie. The hyperglycémie is produced and not diminished, however, when the section below the medulla is followed by section of the cord between the fourth cervical and sixth dorsal. Thus, in these experiments the isolation of the excito-secretory centre of the pancreas (or what we can consider as connected with it, the inhibito-secretory centre of the liver) acts in the same way as does removal of the gland itself. A section just below the medulla, combined with removal of the pancreas, makes no greater hyperglycémie than does simple removal of the gland.

To recapitulate Chauveau's theory: Diabetes is due to an excessive production of sugar by the liver. This production is regulated by the internal secretion of the pancreas, which acts upon the liver through its excito-secretory and inhibito-secretory nerves. The excito-secretory centre is in the cord near the origin of the fourth cervical pair. The inhibito-secretory centre is in the medulla. The internal secretion of the pancreas

acts on these so as to stimulate the inhibito-secretory centre and moderate the excito-secretory centre. Removal of the pancreas does the reverse, and brings on hyperglycémie. Section just below the medulla cuts off the action of the inhibitory centre, and hyperglycémie results. Section of the cord between the fourth cervical and sixth dorsal allows the inhibito-secretory but not the excito-secretory centre to act — whence hypoglycémie. These centres act through ganglia, which, once excited, keep on originating impulses of a similar nature unless they receive an excitation of an opposite character. The removal of the pancreas has the same action on these ganglia as does the section at the junction of the cord and medulla. "The close connection between the effects of depancreatization and those of bulbar section serve to establish the identity of the direct mechanism which presides over the manifestation of these effects. The pancreas plays the rôle of an inhibitor of the liver by means of its central nervous regulators."

This theory of Chauveau's, which I have not stated quite as fully as the author gives it, calls our attention to the unity of diabetes. It is complicated. It is based on analyses of the blood and experiments on the nervous system, both of which methods of experimentation give opportunity for error. Nevertheless, it furnishes a better explanation of all forms of diabetes than anything yet advanced and will be useful in suggesting further work.

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